MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.:65175-R, 65175-E
Early Harvest CMP-D, and Early Harvest CMP-L

From: Lucy D. Markarian, Biologist 9/6/94
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

To: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

Thru: Thomas C. Ellwanger, Section Head 9/12/94
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

Applicant: Nutrachem, Inc.
P.O.Box 607
Delhi, LA 71232

FORMULATION FROM LABEL:

Active Ingredient(s):	65175-R	% by wt. 67175-E
Cytokinins, as Kinetin	1.800 %	0.0825 %
Gibberellic Acid	0.600 %	0.0275 %
Indole Butyric Acid	0.900 %	0.0412 %
Indole Acetic Acid	-------	0.1375 % ← ? New A.I.
Inert Ingredient(s):		
.....		96.700 %
Total:		100.000 %

Generic Data Required also

1/27/94

BACKGROUND

Nutrachem, Inc. Has submitted four studies and a request for the waiver of the inhalation and sensitization tests. The product is a growth regulator and is designed to be used on grain, fruits, and vegetables either by soaking or by spraying. The request for the waiver of the inhalation and sensitization studies had been made before and rejected as of 1/36/94. It is again claimed that the particle size of this granular product is much larger than the sizes inhalable by the test model (53 um), and that under use conditions there is not appreciable probability of inhalation. The sensitization potential is also claimed to be low, since the product is nonirritating to the skin, there is no history of sensitization from similar growth regulating products, and repeated use by handlers and mixers is not likely. Furthermore, it is claimed that the product fits under the Safe Pesticides Policy of EPA. It is stated that testing in these areas not only would not result in usable data, but also would be unnecessary use of animals.

RECOMMENDATION

The submitted tests are found to be supplementary data. PRS reiterates the former position and denies the waiver of the inhalation and sensitization tests once again. A complete battery of test need to be submitted to support the registration. The registrant may also cite tests conducted with substantially similar products, provided that the accession numbers are included and that the tests are acceptable.

65175-R and 65175-E are not similar. One set of tests will not serve to support both products.

The rationale for the classification of the tests is given below.

Acute Oral - Supplementary

1. The test material need not be in solution for intubation as long as the suspension can be made to go through the intubating apparatus. The use of a 1 % solution in no way tests the oral toxicity of a 100 % test material, as toxicity is concentration dependent. It is expected that with solid test materials the product is tested at the highest workable concentration.

2. The use of three doses within 4 hours, and at dose volumes exceeding 1 ml/ 100 is not acceptable. There was no need for this method of intubation. Each dose was between 3.3 to 4.3 ml for animals weighing 202 - 240 g.

3. The loss of test material during intubation was not quantitated. Even if it were, the loss suggests inadequate

intubating technique as well as intubating in greater volumes than acceptable.

4. The absence of any symptoms does not mean that there could not have been any, because the product was so dilute.

5. Weights of the animals should be recorded on a weekly basis.

6. According to the guidelines, necropsy must be performed on all animals.

A new acute oral toxicity test needs to be submitted

Acute Dermal - supplementary

The test material was not properly applied:

1. The test material is to be moistened prior to application to the skin, with the amount of water used specified.

2. It is not specified how the test material was further moistened after application, how much water was used ,or if this amounted to a dilution.

3. The actual site of application is not specified.

4. The dimensions of the patch or the thickness of gauze used is not specified. The gauze should be 2 ply and serve to keep the test material on the site and act as a reservoir during the exposure period.

5. The semiocclusive patch has not been described. The gauze covering of the site should be affixed to the site with hypoallergenic tape, and the trunks of the animals should be wrapped in an impermeable material (rubber dam or plastic sheeting) to retard evaporation and preclude ingestion and inhalation by the test model. A semiocclusive patch is not likely to do this by itself.

6. Care must be taken not to abrade the skin during clipping. The abrasions change the absorption of the test material. Abraded skin is not required by the Agency. (9/10 animals were abraded during shaving).

7. Any dermal irritation must be included in the report. It is not stated when the abrasions healed, if they healed at all, or when the erythema that was observed in one animal was resolved.

8. According to the guidelines, necropsy must be performed on the animals. There was no necropsy.

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A new acute dermal assay must be submitted

Eye Irritation - supplementary

The test material was improperly instilled.

1. According to the guidelines solid test materials are instilled in the eye as solids in 100 mg aliquots. Dissolving the test material in equal amount of water is a dilution and is not acceptable.

2.The source of light, and the means of evaluation: slit lamp, magnification, etc. must be identified.

3. The pre test examination is made with the use of fluorescein dye. It is not stated that this was used at any time.

4. The loss of test material from the eye upon blinking would not have happened with proper instillation. A diluted test material 0.1 g in 0.1 ml water is approximately 0.2 ml. The eye cannot successfully accommodate that volume.

5.If any changes are discernable, they may not be disregarded as negligible. PRS finds moderate circumcorneal hyperemia remarkable, as well as the slight conjunctival redness. According to the Draize scale all the observable changes can be recorded with the appropriate grading. It must never be assumed that an observed change is not large enough to be graded. If it is observed it must be graded with the lowest grade if it is slight.

A new eye test needs to be submitted

Dermal Irritation - supplementary

The test material was improperly applied.

1. The skin should not be clipped more than 24 hrs before application.

2. According to the guidelines the test material needs to be moistened prior to application. Moistening the skin, and moistening the test material after it has been applied is not acceptable. The test material is moistened with a measured amount of water. If this is 1 : 1 or greater, then the reason for the dilution must be explained.

3. The patch should be fully described. If a manufactured patch is purchased, it has to be identified. The gauze cover should not be more than 4 ply. The trunks of the animals are wrapped in an impermeable material to preclude evaporation, and ingestion and inhalation by the test model.
A new primary skin irritation test needs to be submitted.

Waivers

PRS reiterates the previous position and denies the request for the waiver of the inhalation and sensitization tests.

As the test material is to be sprayed as one means of application, it is important to know what the inhalation potential of the test material is. The registrant will market the product as a powder, and cannot control the product after it has been sold. The possibility of the creation of "fines" is present. Powdered test materials are required either to be ground fine, compacted under pressure, and an aerosol generated with a dust generator, or, if soluble, they may be dissolved to create a test atmosphere by atomization, to reach a chamber concentration of currently acceptable limit of 2.0 mg/l, with an MMAD of 4.0 um or preferably less. In either case the inhalation hazard potential is tested. Unless PRS is shown that a test atmosphere cannot be generated by either grinding and attempting to generate a test atmosphere or dissolving the formulation and nebulizing it, and determining the particle size, an inhalation test needs to be submitted. The registrant may also cite tests that are conducted with substantially similar products. In this case accession numbers have to be included.

If the individual components of the test material are claimed to be nontoxic, the registrant cannot assume that the combination of the ingredients cannot have a cumulative toxic effect.
The submitted tests, are considered supplementary data, cannot demonstrate that the subject product is not toxic at all. Even if the test material had been shown to be non toxic by the tested routs, it does not necessarily follow that it is also safe via the inhalation route.

The subdivision M of the guidelines also require a sensitization test for the registration of biochemical pesticides. While it may be said that nonirritating materials generally do not cause sensitization, this is not applicable to all, inclusively. Nonirritating biochemical pesticides can and have induced sensitization in some cases. Stating that mixers and loaders will not be repeatedly exposed to the product is not meaningful. As stated previously the manufacturer has no control over the product after it is sold as a powder, and accidents or repeated misuse is possible. Therefore, a sensitization test must be submitted. PRS, while advocating the judicious use of animals, does not consider the use of animals to show the hazard potential of any formulation unnecessary. The best means of sparing animal life is conducting the studies correctly the first time and using limit tests to best advantage.

LABELING

Precautionary label cannot be recommended without acceptable data. The label will be recommended upon the submission and acceptance of the required tests.

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DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager: 22
MRID No.: 432245=02
Testing Facility: Biocon, Inc.
Author(s): Richard Schuman
Species: Rat, Sprague Dawley
Age: M 53 days, F 71 days
Weight: M 237 - 257 g, F 202 - 238 g
Source: Sasco, Inc., Omaha, NE
Test Material: CMP-D, lot 93147 fine brown powder
Quality Assurance (40 CFR §160.12): Included, adequate

Reviewer: L. Markarian
Report Date: 9/1/93
Report No. 93-023

Conclusion:

1. **The estimated LD_{50} is**
2. **Tox. Category:** **Classification:** Supplementary

Procedure (Deviations from §81-1):

The test material was diluted to 1 % in deionized water for intubation. This was supposed to be the limit of solubility in water. The test material was administered in three doses during a period of 4 hrs to fasted animals by gavage. Water was withdrawn during this period. Two rats appeared to have lost 0.1 ml of test material during the second dosing(not quantified). One animal showed rocking activity at the second dosing, but appeared normal at the third. Observations were daily for 14 days. Body weights were recorded at initiation and termination. There was no necropsy.

Results:

Dosage	(Number Killed/Number Tested)		
	Males	Females	Combined
5000 mg/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

No symptoms were observed. There was no necropsy.

E

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager:22 **Reviewer:** L. Markarian
MRID No.: 432245-03 **Report Date:**9/1/93
Testing Laboratory: Biocon. Inc. **Report No.:**93-026
Author(s): Richard F. Schuman
Species: Rabbit, New Zealand White
Weight:M 2.56 - 2.90 k, F 2.71 - 3.00 k
Age: 12 - 14 weeks
Source: Hazleton Research Products, Denver, PA
Test Material:CMP-D, lot 93147 fine brown powder
Quality Assurance (40 CFR §160.12): Included, adequate

Summary:

1. **The estimated LD_{50} is**

3. **Tox. Category:** **Classification:**Supplementary

Procedure (Deviation From §81-2):

The test material was applied on moistened clipped skin. The test material was moistened further after application (not stated how and with how much water). The site was covered with gauze (thickness not stated), and semiocclusive patch (not described). Collars were placed around the necks. At 24 hrs the collars and patches were removed. One of the animals was treated 24 hrs before the rest of the animals. Observations were made daily. Body weights were recorded at initiation, on day 6, and termination. There was no necropsy.

Results:

Reported Mortality

DOSAGE	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000 mg/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

9/10 animals showed skin abrasions representing razor burns day after application at the test sites. Two rabbits showed red eyes with the nictitating membranes exposed. 1/10 animals showed small patch of erythema (unspecified intensity) on the test site
It is not stated when the redness was resolved, or when the abrasions healed, or if there was any erythema in conjunction with the abrasions.
No necropsy was performed.

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DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: 22
MRID No.: 432245-04
Testing Laboratory: Biocon, Inc.
Author(s): Richard F. Schuman
Species: Rabbit, New Zealand White
Sex: Female
Weight: 2.79 - 3.46
Source: Hazleton Research Products, Denver, PA
Dosage: 0.1 g dissolved in 0.1 ml water
Test Material: CMP-D, lot 93147 fine brown powder
Quality Assurance (40 CFR §160.12): Included, Adequate

Reviewer: L. Markarian
Report Date: 8/20/93
Report No.: 93-024

Summary:

1. **Toxicity Category:**

2. **Classification:** Supplementary

Procedure (Deviations From §81-4):

The eyes of the rabbits were examined by a veterinary ophthalmologist four hours prior to the instillation of the test material. 0.1 g aliquots of the test material were dissolved in 0.1 ml of deionized water and instilled in the conjunctival sacs of the eyes. Observations were at 1, 24, 48 and 72 hours according to Draize. The source of light or the means of observation is not stated. No fluorescein was used to confirm corneal findings.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	0/6	0/6	0/6	0/6				
Iris	0/6	0/6	0/6	0/6				
Conjunctivae	0/6	0/6	0/6	0/6				
Redness								
Chemosis								
Discharge								

Comments:

It is stated that some of the instilled test material was blinked out of the eye. It is estimated that between 15-30 microliters

were blinked out.
At one hour although slight to moderate circumcorneal hyperemia and conjunctival redness was observed in two eyes, the changes were so slight that it was not reported as positive reactions.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager:22
MRID No.: 432245-05
Testing Laboratory: Boicon, Inc.
Author(s): Richard F. Schuman
Species: Rabbit, New Zealand White
Age:14 weeks old
Sex: Male
Weight:3.1 - 3.4 K
Dosage:0.5 g
Test Material:CMP-D, lot 93147 fine brown powder
Quality Assurance (40 CFR §160.12):included, adequate

Reviewer: L. Markarian
Report Date:8/22/93
Report No.:93-025

Summary:

1. **The Primary Irritation Index =**
2. **Toxicity Category:**
3. **Classification:**Supplementary

Procedure (Deviations From §81-5):

The rabbits were clipped 24- 36 hrs before application. Dry test material was applied to moistened skin of the animals on a 6 cm^2 area. The test material was further moistened after application (it is not stated how this was done). The site was covered with gauze and semioccluded patch and collars were placed around the necks. At 4 hrs the patches were removed and the sites cleaned of any residue. Observations were according to Draize at 30 minutes and at 24, 48 and 72 hrs.

Results:

No reaction was observed at any site at any interval.

Special Comments:

Tox Chem No: 116801 Cytokinin
046701 IBA
043801 Gibberellic Acid

Current Date: 9/6/93

Laboratory: Biocon, Inc.,15801 Crabbs Branch Way, Rockville, MD 20855

S T U D Y	M A T E R I A L	MRID NO	R E S U L T S	TOX CAT	CORE GRADE
Acute Oral Limit Test(Rats) 93-023 9/1/93	CMP-D Lot 93147	432245-02			Supplementary
Acute Dermal Limit Test(Rabbits) 93-026 9/1/93	" " "	432245-04			Supplementary
Eye Irritation in Rabbits 93-024 8/20/93	" " "	432245-04			Supplementary
Dermal Irritation in Rabbits 93-025 8/22/93	" " "	432345-05			Supplementary